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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-------------------------------------|-------------|----------------------|-------------------------|------------------|
| 10/084,555 | 02/25/2002 | Michael G. Goggins | JHU1700-1 | 7972 |
| 28213 | 7590 | 09/06/2005 | EXAMINER | |
| DLA PIPER RUDNICK GRAY CARY US, LLP | | | WILDER, CYNTHIA B | |
| 4365 EXECUTIVE DRIVE | | | ART UNIT | PAPER NUMBER |
| SUITE 1100 | | | | 1637 |
| SAN DIEGO, CA 92121-2133 | | | DATE MAILED: 09/06/2005 | |

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | |
|------------------------------|--------------------------------------|------------------|
| Office Action Summary | Application No. | Applicant(s) |
| | 10/084,555 | GOGGINS ET AL. |
| | Examiner Cynthia B. Wilder, Ph.D. | Art Unit 1637 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 17 June 2005.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 7,8,11-14,22 and 23 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) 7,8,11-14 and 23 is/are allowed.

6) Claim(s) 22 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. _____.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

| | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____. | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____. |

FINAL ACTION

1. Applicant's amendment filed June 17, 2005 is acknowledged and has been entered. Claims 7 and 14 have been amended. Claims 1-6, 9-10 and 15-21 have been canceled. Claims 7-8, 11-14, 22 and 23 are pending. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made FINAL

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Previous Rejections and objections

3. The object to the specification under 35 USC 132 is maintained and discussed below. The prior art rejection under 35 USC 112 second paragraph directed to claims 7-8, 12-14 and 22-24 for lacking enablement is withdrawn in view of Applicant's amendment. The New matter rejection directed to claim 22 is maintained and discussed below.

Specification

4. Once again, the amendment filed August 4, 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The substitute raw sequence listing and computer readable format of the sequence listing is objected to because the sequences listed as SEQ ID NO: 115 through 118 are not supported by the specification as originally filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112: New Matter

5. Once again, claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim 22 is drawn to a method of claim 12, wherein the primers pairs are selected from SEQ ID NOS: 115, SEQ ID NO: 116 and SEQ ID NO: 117, SEQ ID NO: 1118. The sequences recited as SEQ ID NOS: 115-118 are not supported by the specification as originally filed. Nowhere in the specification is there a teaching of the sequences recited as SEQ ID NOS: 115-118. Applicant does not provide any cited support for the newly added sequences and only state in remarks filed on August 4, 2003 that these sequences were derived from SEQ ID NO: 8. However and alignment and search of SEQ ID NO: 8 show very little to no sequence homology between the sequence recited in SEQ ID NO: 8 and the newly added sequences SEQ ID NOS: 115-118. There is no evidence provided anywhere in the specification or raw sequence listing as originally filed to suggest to one that these sequences recited in SEQ ID NOS: 115-118 were originally present. Therefore, the specification would not have suggested to the skilled artisan that the applicant was in possession of the claimed invention as of the filing date of the application.

Applicant's Traversal

6. Applicant traverses the rejections on the following grounds: Applicant states that one skill in the art viewing the current disclosure at the time of filing would have been able to

identify unmethylated and methylated sequence primers given the short nucleic acid sequence of ppENK provided in SEQ ID NO: 8 or in the public database, including those primer set forth as SEQ ID NOS: 115-118. Applicant states that methods for detecting aberrant methylation of a gene are described in the specification which include processing steps, prior to PCR amplification, that results in predictable alterations in nucleic acid structure. Applicant states that in particular, the specification exemplifies using methylation-specific PCR (MSP), including bisulfite modification and bisulfite-modified genomic sequencing. Applicant states that chemical modifications of a nucleic acid by bisulfite treatment includes modification of unmethylated cytosine to uracil, while methylated residues are resistant to such modifications. Applicant continues to explain the process of bisulfite treatment and provides Exhibit A and B to illustrate the concept. Applicant states that as such, one of skill in the art would not expect primers used for PCR analysis of a nucleic acid following bisulfite treatment to be limited to primer sequences having exact homology with the sequence not subjected to bisulfite treatment. With respect to the claims 115-118 as recited in the claim 22, Applicant contends that one of skill in the art, viewing the current disclosure at the time of filing, would have been able to design and test unmethylated and methylated sequence primers given the short nucleic acid sequence of ppENK provided in SEQ ID NO: 8 or the public databases, including those primers set forth as SEQ ID NO: 115-118. Applicant respectfully request the rejections be withdrawn.

Examiner's Response

7. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follows: In regards to applicant's arguments that one of skill in the art would be able to identify unmethylated and methylated sequence primers given the short

nucleic acid sequence of ppENK provided in SEQ ID NO: 8 or the public database, it is noted that an alignment of the primers recited in SEQ ID NO: 115-118 did not reveal any significant homology, thus clearly indicating that the primers were not derived from SEQ ID NO: 8 as claimed. In regards to Applicant's arguments that the sequences could be found by searching the public database, it is noted that MPEP 2421.02 states that "the sequence rules embrace all unbranched nucleotide sequences with ten or more bases and all unbranched, non-D amino acid sequences with four or more amino acids, provided that there are at least 4 "specifically defined" nucleotides or amino acids. The rules apply to all sequences in a given application, whether claimed or not. All such sequences are relevant for the purposes of building a comprehensive database and properly assessing prior art. It is therefore essential that all sequences, whether only disclosed or also claimed, be included in the database".

In regards to Applicant's arguments concerning detection by bisulfite treatment, it is noted that such arguments does not satisfy the new matter required under 35 USC 132 which states that **no amendment shall introduce new matter into the disclosure of the invention** regardless to whether it would be easily isolated or not by one of skill in the art. Further MPEP 2422.07 states the following: "The requirement to submit a statement that a submission in reply to the requirements of this section does not include new matter or matter which goes beyond the disclosure in the application as filed is not the first instance in which the applicant has been required to ensure that there is not new matter upon amendment. The requirement is analogous to that found in 37 CFR 1.125 regarding substitute specifications. When a substitute specification is required because the number or nature of amendments would make it difficult to examine the application, the applicant must include a statement that the substitute specification includes no

new matter. The necessity of requiring a substitute “Sequence Listing,” or pages thereof, is similar to the necessity of requiring a substitute specification and, likewise, the burden is on the applicant to ensure that no new matter is added. Applicants have a duty to comply with the statutory prohibition (35 U.S.C. 132 and 35 U.S.C. 251) against the introduction of new matter. It should be noted that the treatment accorded errors in sequencing or any other errors prior to the implementation date of the sequence rules will be no different for those applications filed on or after the implementation date of these rules. The correction of errors in sequencing or any other errors that are made in describing an invention are, as they have always been, subject to the statutory prohibition (35 U.S.C. 132 and 35 U.S.C. 251) against the introduction of new matter. Applicant's arguments are not sufficient to overcome the rejections noted above. Accordingly, the rejections under 35 USC 132 and 35 USC 112 first paragraph are maintained.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

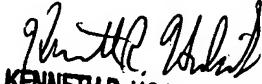
9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.


KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
8/30/05